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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/407,430	09/29/1999	HOWARD J. WORMAN	0575/54805	2750

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/407,430	Applicant(s) WORMAN ET AL.	
	Examiner Quang Nguyen, Ph.D.	Art Unit 1636	

--The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

THE REPLY FILED 21 February 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 2 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☒ they raise the issue of new matter (see Note below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1,3,5,7,10 and 11*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 2. NOTE: The scope of the new claims 44-49 is no longer directed to a method for treating or preventing hepatitis C virus infection in a subject, and instead the new claims are drawn to a method of preventing attachment of hepatitis C virus onto a cell which may require further consideration regarding to enablement issues. It is noted that "preventing attachment" recited in the preamble of new claims is not the same as "inhibiting attachment" which is required for treating or preventing hepatitis C virus infection in a subject. Additionally, it is unclear what is encompassed by the phrase "contacting the cell with an effective amount of an Eo protein having amino acids 1-120 of SEQ ID NO:1 to the subject" recited in the new claims. This is not necessarily limited to administering an effective amount of an Eo protein having amino acids 1-120 of SEQ ID NO:1 to a subject. The new claims could encompass presenting to a subject with a cell already contacted with an effective amount of the Eo protein. Accordingly, since the new claims raise new issues for consideration, and they fail to further reducing or simplifying issues for appeal, the proposed amendments will not be entered.

Continuation of 5. does NOT place the application in condition for allowance because: Applicants' arguments in amendment C filed 2/21/02 are respectfully found to be unpersuasive for the following reasons.

As noted in the Final Office Action, the instant specification fails to teach or demonstrate a correlation or a nexus between the binding interaction of the Eo protein having SEQ ID NO:1 and the Eo1 protein (containing amino acids 1-120 of SEQ ID NO:1) with a portion of the hepatitis C virus E2 envelope protein observed via a yeast two hybrid assay with any of the therapeutic effects contemplated by Applicants (e.g., inhibition of HCV replication, stopping or delaying the progression of liver disease in a subject). The prior art at the filing date of the present application does not provide such guidance. Additionally, the standard treatments for patients infected with hepatitis C at the filing date of this application are not based on the inhibition of hepatitis C attachement onto cells (See Gish, Cited previously). The physiological art is also recognized to be unpredictable. Given the lack of sufficient guidance provided by the instant specification, it would require undue experimentation for one skilled in the art to make and use the methods as claimed.

Applicants mainly argued that the application clearly shows that Eo protein binds with the E2 envelope protein of HCV, and since E2 has been shown to bind plasma membranes of cells and that this action of E2 mediates entry to the HCV virus into the cells; therefore, it is reasonably to expect that Eo protein to block HCV attachment and entry into cells, similar to the action of antibodies to E2 as evidenced by the teachings of Rosa et al.; Yi et al. and Flint et al. (Cited previously). Thus, the enablement rejection should be withdrawn.

Examiner would like to state that the binding of Eo with E2 envelope protein of HCV shown in the present application has not been shown or demonstrated to be similar to the action of neutralizing antibodies to E2 protein, and therefore the expected desired results (e.g., blocking HCV attachement and entry into cells effective to yield contemplated treatment and prophylactic effects) would not be reasonably expected. The following are reasons that raise doubt to Applicant's arguments.

(1) There is no evidence of record indicating or suggesting that Eo binds to the E2 envelope protein at the same epitopes as the reported neutralizing antibodies. Which particularly amino acid residues on the E2 envelope protein being recognized by the Eo protein of the presently claimed invention? Certainly, the whole amino acid sequence of residues 384 to 661 in E2 envelope protein does not constitute a neutralizing epitope (please check the definition of an epitope). Without knowing or teaching this relevant information, then how one can assert or certain that Eo can bind to the same neutralizing epitopes recognized by antibodies to inhibit or block HCV attachment or entry into the cells?

(2) It should be noted that the binding between the Eo and E2 envelope proteins was observed in yeast cells. That means that Eo protein of the presently claimed invention recognizes E2 envelope protein produced in yeast cells. However, Rosa et al. clearly demonstrated that E2 proteins expressed in yeast or insect cells are not capable of binding to human cells (see abstract and Fig. 1). This is in contrast to the ability of E2 protein expressed in mammalian cells to bind to human cells with high affinity. This suggests that conformation of E2 proteins derived from different sources may be variable and different. Additionally, Rosa et al. also noted that vaccination with recombinant envelope proteins expressed in yeast or insect cells fail to protect chimpanzees from primary infection by an homologous HCV isolate (page 1761, col. 2, top of first full paragraph). As such, how then a simple binding interaction between Eo protein and E2 envelope protein observed in yeast cells can be reasonably extrapolated to a similar interaction between a neutralizing antibody and E2 envelope protein to prevent HCV infection in vivo? There is no evidence of record indicating that Eo protein is also capable of binding to the E2 envelope protein derived from cellular sources other than yeast cells.

(3) With the lack of guidance provided by the instant specification regarding to the aforementioned issues, then how can one reasonably expect the Eo protein can disrupt the E1/E2 heteromeric complex that is thought to be necessary for HCV binding and entry to the cells? Unlike the simple scenerio presented by Applicants that upon binding to the E2 envelope protein by the Eo protein of the present invention, then E2 could not bind to E1 to form the heterodimeric complex, it is noted that the claimed method is not a simple in vitro binding method of mixing different components in a test-tube. The endogenous E1/E2 heteromeic complex is already present in the HCV (see Final Office, page 9, lines 8-14) , the how a simple application of Eo protein of the instant invention can disrupt such endogenous E1/E2 heteromeric complex to prevent HCV binding and subsequent cell infection, especially critical information regarding to the biochemical binding properties of the Eo protein to mammalian expressed E2 protein has yet been determined.

Accordingly, the pending claims remain rejected for the reasons of record.

DAVE T. NGUYEN
PRIMARY EXAMINER